

REMARKS

Claims 1-15 are pending in the present application.

Claims 1 and 14 provide, in part, a novel crystal form of N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine methyl ester (Neotame), which exhibits a characteristic X-ray diffraction peak at a diffraction angle,  $2\theta$ , measured using a  $\text{CuK}\alpha$  rays of about  $7.1^\circ$  (referred to hereinafter as “C-type crystals” or the “C-type crystal form”).

Present Claim 2 relates to a process for producing such crystals. Present Claims 3, 4, and 15 relate to granules which contain C-type crystals of Neotame, and present Claims 5-13 relate to compositions which contain C-type crystals of Neotame.

The C-type crystals of the present claims are distinct from the A-type crystals afforded by one of the cited references (i.e., Nofre et al). Moreover, the inventors have surprisingly found that the presently claimed crystals exhibit an increased rate of dissolution in water, as compared to A-type crystals, even though the C-type crystals contain less water than the A-type crystals. Further, none of the art of record, individually or in combination, provide reasonable guidance to lead the artisan to (a) foresee the presence of the C-type crystals of Neotame, (b) foresee the advantageous properties flowing from the C-type crystals of Neotame, or (c) provide any guidance as to how one of skill in the art would obtain the C-type crystals of Neotame. Accordingly, the art of record, individually or in combination, cannot affect the patentability of the present claims.

Reconsideration is requested in view of the following comments.

The rejection of Claims 1-15 under 35 U.S.C. § 103 (a) in view of U.S. patent No. 4,810,818 (Wakamatsu et al) in further view of U.S. Patent No. 5,480,668 (Nofre et al) is traversed.

As routinely conceded by the Examiner, most recently on page 2 of the Official Action dated August 26, 2003 (paper number 24), Wakamatsu et al is concerned only with Aspartame and is completely silent in regard to Neotame. Nofre et al discloses certain derivatives of Aspartame, including Neotame. However, there is no teaching in Nofre et al of the presently claimed C-type crystals. In fact, as shown in the Declaration of Nagashima filed on September 21, 2001, the Neotame produced according to Nofre et al exists in either an amorphous state or as A-type crystals (a fact that remains undisputed).

On November 19, 2002, Applicants filed the Declaration of Kashiwagi, which stated that polymorph or pseudopolymorph related crystal forms exhibit different physical properties that can have a large influence on the industrial processing of the compound (see paragraph 5). Moreover, the discovery of a new crystal form of a known compound not only is unexpected (a fact supported by the attached Declaration of Professor Jerry Atwood), but also can be commercially important. In fact, no prior art reference has been cited which stands for the proposition that the mere existence of one crystal form for a given compound would suggest the existence of another, different crystal form for that compound (a fact conceded by the Examiner at page 5, paragraph (e) of paper number 22).

As stated above, the presently claimed invention relates to C-type crystals of Neotame. The art of record neither discloses nor suggests this specific crystal form. The Examiner ignores the holdings in In re Certain Crystalline Cefadroxil Monohydrate, 15 USPQ2d 1263 (US ITC 1990) and In re Cofer, 148 USPQ 268 (CCPA 1966), which are part of a long-held precedent that a new crystalline form of a compound is *not* obvious absent

evidence that “the prior art suggests the *particular structure or form* of the compound or composition *as well as* suitable methods for obtaining that structure or form.” Despite the foregoing, the Examiner continues to maintain that the “very close structural similarity of Neotame and Aspartame and the large overlap in their chemical and physiological behavior and intended uses the expectation for success would have been reasonable.” (paper number 24, page 3) However, in so doing, the Examiner appears to insert his own perception of what would be known to the skilled artisan in place of that which the skilled artisan would *actually* know.

To demonstrate the level of skill in the art (*i.e.*, the state of the art relating to polymorphs and pseudopolymorphs) and the corresponding lack of “expectation of success” based on the art of record, Applicants **submit herewith** a Declaration of Professor Jerry Atwood (“Atwood Declaration”).

As is clearly evident by Appendix A of the Atwood Declaration, Professor Atwood is highly published and has received numerous awards in the field of the present endeavor. From 1985 to 1998, Professor Atwood was Editor of the *Journal of Chemical Crystallography*. In 1999 he was named Consulting Editor for the *Journal of Chemical Crystallography*. He has edited the *Journal of Supramolecular Chemistry* since 2000, and has been Associate Editor of *Chemical Communications* since 1996. From 1992 until 2000, Professor Atwood was editor of *Supramolecular Chemistry*. From 1985 to 1993, he was Regional Editor for the *Journal of Coordination Chemistry*. Professor Atwood is co-Editor of the *Inclusion Compounds* book series (five volumes), *Comprehensive Supramolecular Chemistry* (ten volumes) and the *Encyclopedia of Supramolecular Chemistry* (two volumes). He currently serves on the Editorial Boards of *Crystal Growth & Design*, *Crystal Engineering*, the *New Journal of Chemistry*, *Supramolecular Chemistry*, and the *Journal of*

*Coordination Chemistry*. Professor Atwood has published more than 500 articles in refereed journals, has authored ten patents, and is an expert in the fields of crystal growth, crystal engineering, and polymer chemistry.

As stated in paragraph 11 of the Atwood Declaration, many organic compounds crystallize in more than one form (i.e one organic compound may crystallize in two or more different forms). These forms are not different in the way in which the atoms of the molecule are connected, but rather in the manner in which the molecules relate to each other in the crystalline state. This behavior is referred to as polymorphism. Polymorphs and pseudopolymorphs may have very different physical properties such as melting point, dissolution rate, solubility, particle size, and hygroscopicity (paragraph 12 of the Atwood Declaration). One polymorph may be much more useful for a given purpose than is another polymorph, even though, chemically, the molecules are the same.

In paragraphs 13 and 14 of the Atwood Declaration, Professor Atwood summarizes that it is *not possible* to predict polymorphism. He further states that once polymorphs have been discovered, it is necessary to describe the methods and conditions of crystallization that will afford reproducibility. Therefore, it is not sufficient to simply state that a compound is crystallized from a given solvent. Polymorphs may be obtained even from the same solvent under different crystallization conditions (paragraph 14 of the Atwood Declaration).

In fact, Professor Atwood points out that some chemical compounds do not exhibit polymorphism (paragraph 15 of the Atwood Declaration). Citing J. Bernstein, *Polymorphism in Molecular Crystals*, (2002), Professor Atwood notes that “The *possibility* of polymorphism may exist for any particular compound, but the conditions required to prepare as yet unknown polymorphs are by no means obvious. There are as yet no comprehensive systematic methods for feasibly determining those conditions. Moreover, we are almost totally ignorant

about the properties to be expected from any new polymorphs that might be obtained.”  
(paragraph 16 of the Atwood Declaration) It should now be clear to the Examiner, as is readily apparent to the skilled artisan, that the mere existence of one or more crystalline forms for a given compound bears no relevance on the existence of further crystalline forms for that compound or the existence of *any* crystalline forms for an analogous compound. Therefore, the method by which a particular polymorph may reproducibly be obtained is as novel as the polymorph itself.

Furthermore, the Examiner’s attention is directed to paragraphs 19-31 in which Professor Atwood discusses, at length, the differences between the previously reported A-type crystals of Neotame and the claimed C-type crystals of Neotame as further supported by the Nagashima Declaration. On the basis of this discussion and the state of the art as defined in paragraphs 11-19 of the Atwood Declaration, Professor Atwood opines “

In my opinion, the existence of two types of crystals of Aspartame does not mean that two types of crystals will exist for Neotame. The functionality of Aspartame and Neotame is similar in that they both possess the L-aspartyl-L-phenylalanine methyl ester core structure. However, the presence of the bulky dimethylbutyl group on Neotame means that the crystallization behavior of Neotame will in all likelihood be different from that of Aspartame. *This means that prediction of Neotame crystallization behavior based on that of Aspartame is not backed up by sound science.* The existence of polymorphs or pseudopolymorphs of Neotame must be determined by experimentation, not by analogy to Aspartame. (*emphasis added*, paragraph 32 of the Atwood Declaration)

Accordingly, Applicants ask: If one of skill in the art deems the existence of a polymorph and the method by which the polymorph is obtained to be novel and unobvious in view of the art of record, how can one of less than the requisite skill consider it to be anything else? In addition, if one of skill in the art recognizes that “sound science” does not support the prediction of crystallization behavior of a compound based on the crystallization behavior


of a distantly related compound, then how can the art of record render the claimed invention obvious?

In view of the foregoing, as further supported by the enclosed Atwood Declaration, Applicants request withdrawal of this ground of rejection.

Applicants submit that the present application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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